Otic Anti-Infective/Anesthetic

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS[1,2]

Drug Name	Manufacturer	Indication(s)
acetic acid (Vosol®)	generic	For the treatment of otitis externa
acetic acid / hydrocortisone (Acetasol HC, Vosol® HC)	generic	For the treatment of otitis externa
acetic acid in aluminum acetate	generic	For the treatment of otitis externa
acetic acid/ antipyrine/ benzocaine/ polycosanol (PR Otic®)	PruGen	Acute otitis media of various etiologies ▪ Prompt relief of pain and reduction of inflammation in the congestIve and serous stages. ▪ Adjuvant therapy during systemic antibiotic administration for resolution of the infection. ▪ To facilitate the removal of excessive or impacted cerumen
antipyrine/ benzocaine (Auralgan®, Aurodex®, Auroguard®, Dolotic®)	generic	▪ For the treatment of otitis externa ▪ To facilitate the removal of excessive or impacted cerumen
antipyrine/ benzocaine/ polycosanol (Otic Care®)	Pur Tek	Acute otitis media of various etiologies ▪ Prompt relief of pain and reduction of inflammation. ▪ Adjuvant therapy during systemic antibiotic administration for resolution of the infection. ▪ To facilitate the removal of excessive or impacted cerumen
antipyrine/ benzocaine/ glycerin/ zinc (Neotic®, Otozin™)	Arbor, Allegis	Acute otitis media of various etiologies ▪ Prompt relief of pain and reduction of inflammation in the congestIve and serous stages. ▪ Adjuvant therapy during systemic antibiotic administration for resolution of the infection. ▪ To facilitate the removal of excessive or impacted cerumen
benzocaine (Pinnacaine®)	Sircle	For the relief of minor ear pain and itching
chloroxylenol / benzocaine / hydrocortisone (Myoxin®, Trioxin®)	GM Pharmaceuticals, Vertical Pharmaceuticals	For the treatment of otitis externa complicated by inflammation and to control pruritus in the auditory canal
chloroxylenol/ pramoxine (Pramotic®)	Hawthorn	For the treatment of otitis externa
chloroxylenol/ pramoxine/ hydrocortisone (Pramoxine HC®)	generic	For the treatment of otitis externa

The following products have been discontinued – acetic acid/antipyrine/benzocaine/polycosanol (Treagan®), chloroxylenol/pramoxine/zinc/glycerin (Zinotic®, Zinotic® ES)

OVERVIEW

The standard treatment for acute otitis media (AOM) is the use of systemic antibiotics while topical (otic) therapy antibiotic is recommended for uncomplicated otitis externa.

Acute otitis externa (AOE) is an acute inflammation of the external auditory canal. Commonly referred to as "swimmer's ear" or "tropical ear", this condition is often precipitated by water exposure or trauma. The etiology is typically bacterial; the most common pathogens implicated are *Pseudomonas aeruginosa and Staphylococcus aureus,* often occurring as a polymicrobial infection. Patients will typically complain of otalgia and otorrhea, and the ear canal may appear erythematous and swollen. It is imperative that the ear canal be cleared of any discharge or debris that can occlude the canal since the presence of such material can keep the canal moist and interfere with topical treatment. All ages are affected, with a peak incidence in children aged seven to 12 years.

In 2006, the American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) released guidelines for the management of acute otitis externa (AOE) in patients over two years of age.[3] They recommend the use of topical preparations for initial therapy of diffuse, uncomplicated AOE. Systemic antimicrobial therapy should not be used unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy (e.g., diabetes, immune deficiency, nonintact tympanic membrane, presence of tympanostomy tubes). Management of AOE should include an assessment of pain and analgesic treatment prescribed based on pain severity. Effective topical treatments include otic antibiotics (e.g., aminoglycosides, polymyxin B, quinolones), otic steroids (e.g., hydrocortisone), and low pH antiseptics, (e.g., aluminum acetate or acetic acid).[4]

Evidence supports equivalent results with ear cleansing, an ear wick, and any of the choices of topical agents including acidifying agents, antibiotics, antibiotic and steroid combinations, or antifungal agents.[5] The choice of therapy should be based on efficacy, low incidence of adverse events, and the likelihood of adherence to therapy.[6]

Cerumen impaction is an accumulation of cerumen that causes symptoms or prevents assessment of the ear canal and/or tympanic membrane.[7] Cerumen impaction is more common in the elderly. Excessive cerumen is normally expelled from the ear canal automatically, assisted by motion of the jaw. The AAO-HNSF clinical practice guidelines for cerumen impaction recommend three options for cerumen removal: topical cerumenolytic agents, irrigation, and manual removal other than irrigation. Cerumenolytics, or wax-softening agents, are used to disperse the cerumen and can be used alone or in combination with irrigation or manual removal. The guidelines state that no specific agent is superior to another and none are found to be superior to either saline or water.

PHARMACOLOGY[8,9]

Acetic acid is a low pH antiseptic agent. Its mechanism of action is unknown.

Chloroxylenol, a halogenated phenol, provides topical germicidal activity against gram negative and gram positive bacteria, fungi, and yeast.

Hydrocortisone is a corticosteroid that controls inflammation, edema, pruritus, and other dermal reactions.

Antipyrine, an anti-inflammatory and analgesic agent, exerts its effects by decreasing prostaglandin synthesis.

Benzocaine and pramoxine are local anesthetics that produce a reversible blockade of nerve conduction by decreasing nerve membrane permeability to sodium, leading to a decreased rate of membrane depolarization and increased threshold for electrical excitability.

Polycosanol is an astringent, whose drying effect and removal of debris helps relieve local burning, itching, and irritation.

Glycerin and zinc acetate are topical skin protectants that may also help provide relief to skin surfaces. Zinc also absorbs moisture, thereby acting as a mild astringent.

PHARMACOKINETICS[10]

Due to the topical application of these products, minimal systemic absorption is expected.

CONTRAINDICATIONS/WARNINGS[11,12]

All products in this review are contraindicated in people with hypersensitivity to any of the ingredients contained in the product, and in persons with perforated tympanic membrane or unexplained discharge from the ear.

These agents should be discontinued if sensitization or irritation occurs.

Pain suppression with the use of benzocaine otic preparations (Pinnacaine, Myoxin, Trioxin) may mask the progression of underlying disease.[13] Patients prescribed a topical anesthetic should be re-examined within 48 hours to ensure appropriate response to primary therapy.

Overgrowth of non-susceptible organisms or superinfection may occur with prolonged use of products containing a germicidal agent, such as acetic acid (Vosol, Vosol HC, Otic Care, PR Otic) or chloroxylenol (Myoxin, Trioxin, Pramotic, Pramoxine HC).

Studies evaluating cerumenolytics excluded patients with otitis externa; therefore, cerumenolytics should be avoided in patients with active infections of the ear canal.[14]

These agents are for otic use only. Avoid accidental exposure to the eyes.

DRUG INTERACTIONS[15]

No clinically relevant drug-drug interactions are expected with agents in this review when used as an otic agent.

ADVERSE EFFECTS[16,17]

The products in this review are generally tolerated well; however, stinging, burning local irritation, contact dermatitis, or hypersensitivity reactions can occur.

Topical benzocaine may cause contact dermatitis that can worsen or prolong otitis externa.

Discontinue treatment if signs and symptoms (e.g., burning, pruritus, redness, or oozing sores in ear) of a local allergic reaction occur.

Warming an otic product by holding the bottle in hand for one to two minutes may minimize dizziness and pain on application; do not heat above body temperature.

SPECIAL POPULATIONS[18,19]

Pediatrics

Children may absorb proportionally larger amounts of topical corticosteroids, such as hydrocortisone (Myoxin, Pramoxine HC, Trioxin, Vosol HC) and, therefore, may be more susceptible to systemic toxicity, such as HPA axis suppression and Cushing's syndrome. Pediatric patients should be given the least amount needed for an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

Safety and effectiveness of acetic acid containing products (Vosol, Vosol HC, PR Otic) in pediatric patients below the age of three years have not been established.

Do not use benzocaine (Pinnacaine) in infants under one year of age.

The safety and efficacy of chloroxylenol/hydrocortisone/pramoxine otic combinations (Pramoxine HC) has not been established in infants.

Dosing regimens for use in infants and children are available for chloroxylenol/benzocaine/hydrocortisone (Myoxin, Trioxin). Dosing regimens for use in children are available for antipyrine/benzocaine, antipyrine/benzocaine/polycosanol (Otic Care, PR Otic), and antipyrine/benzocaine/zinc (Neotic, Otozin).

Pregnancy

All agents in this review are classified as Pregnancy Category C.

DOSAGE AND ADMINISTRATION[20,21]

Drug	Indication/Dosages	Package size
acetic acid (Vosol)	Instill four to six drops into ear canal(s). Repeat every two to three hours.	2% - 15 mL
acetic acid / hydrocortisone (Acetasol HC, Vosol HC)	Insert a cotton wick into the ear canal and saturate with medication. Keep wick moist by adding three to five drops every four to six hours. May remove the wick after 24 hours and continue to instill three to five drops into the ear canal(s) three to four times per day. The lower end of the dosage range is usually recommended in children.	2% /1% - 10 mL
acetic acid in aluminum acetate	Instill four to six drops into the ear canal(s). Repeat every two to three hours.	2% - 60 mL
acetic acid/ antipyrine/ benzocaine/ polycosanol (PR Otic)	**Acute otitis media:** Fill ear canal(s) with medication. Repeat every one to two hours until pain and congestion are relieved. **Removal of cerumen:** Instill in ear canal three times daily for two to three days.	0.01% / 5.4% / 1.4% / 0.01% - 14 mL

Dosage and Administration (continued)

Drug	Indication/Dosages	Package size
antipyrine/ benzocaine (Auralgan®, Aurodex®, Auroguard®, Dolotic®)	**Otitis externa:** **Adults:** Instill two to four drops into ear canal(s); Repeat three to four times per day, or up to once every one or two hours. **Children:** Fill ear canal(s) with medication; Repeat every one to two hours as needed for ear pain. **Removal of cerumen:** **Adults, Adolescents and Children:** Instill drops into ear canal(s) three to four times per day for two to three days.	5.4% / 1.4% - 10 mL, 15 mL
antipyrine/ benzocaine/ polycosanol (Otic Care®)	**Acute otitis media:** **Adults, Adolescents, and Children:** Fill ear canal(s) with solution; insert cotton pledget moistened with medication. Repeat every 1—2 hours as needed for ear pain. **Removal of cerumen:** **Adults, Adolescents, and Children:** Instill 3 times daily for 2—3 days, then insert a cotton pledget moistened with medication.	5.4% / 1.4% / 0.0097% - 14 mL,
antipyrine/ benzocaine/ zinc (Neotic, Otozin™)	**Acute otitis media:** Fill ear canal(s) with medication. Repeat every one to two hours until pain/congestion is relieved. **Removal of cerumen:** Instill in ear canal(s) three times daily for two to three days.	5.4%/ 1%/ 1% - 10 mL x 2
benzocaine (Pinnacaine)	Instill four to five drops into ear canal(s). May repeat repeated every one to two hours, as needed.	20% - 15mL
chloroxylenol / benzocaine / hydrocortisone (Myoxin, Trioxin)	**Adults and adolescents:** Instill four to five drops into ear canal(s) three to four times per day. Maximum of 20 drops per day. **Infants and children:** Instill three drops into ear canal(s) three to four times per day. For larger children may consider four to five drops three to four times per day. Maximum of 20 drops per day for children, 12 drops per day for infants	0.1%/ 1.5%/ 1% - 15 mL
chloroxylenol/ pramoxine (Pramotic)	**Adults:** Instill four to five drops into ear canal(s) three to four times per day. **Pediatric:** Instill three drops into ear canal(s) three to four times per day.	0.1%/ 1% - 10 mL
chloroxylenol/ pramoxine / hydrocortisone (Pramoxine HC)	Instill three to five drops into ear canal(s) three to four times per day.	0.1%/ 1%/ 1% - 10 mL

Patients should be instructed to remain still while medication is in the ear canal for three to five minutes.[22]

If obstruction in the ear canal is evident, aural cleansing (aural toilet) to remove obstructing debris and placement of a wick, if edema prevents drug delivery, should be considered. [23]

In general, it is recommended that drops be given for three days beyond the cessation of symptoms (typically five to seven days); however, in patients with more severe infections, 10 to 14 days of treatment may be required.[24]

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and the FDA-approved indications. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Limited comparative clinical trials were found.

acetic acid versus triamcinolone/acetic acid versus dexamethasone/neomycin/polymyxin

In a double-blind trial, 213 adults with acute otitis externa were randomized to receive acetic acid, 0.1% triamcinolone acetonide and acetic acid, or 0.66 mg dexamethasone phosphate sodium, 5 mg neomycin sulphate, and 10,000 IU polymyxin B sulphate/mL.[25] Each patient received three drops of the study preparation three times daily. The primary outcome measure was the duration of symptoms in days until recovery according to the patient diary entries. Secondary outcome measures were the cure rate at days six-eight, 13-15, and 20-22 and the recurrence of symptoms between days 21 and 42. The median duration to recovery differed between the treatment arms: 8 days (95% CI; 7 to 9) in the acetic acid group, 7 days (5.8 to 8.3) in the steroid and acetic acid group, and 6 days (5.1 to 6.9) in the steroid and antibiotic group. The overall cure rate for all treatment groups after 7, 14, and 21 days was 40, 72, and 79 percent, respectively. Otoscopic signs were not significantly different between treatment arms. Significantly more patients in the acetic acid group had recurrence of symptoms between days 21 and 42 and more severe symptoms than in the other two groups.

aluminum acetate versus gentamicin

The clinical efficacy of the topical antiseptic, aluminum acetate, and the topical antibiotic, gentamicin, was compared for the initial treatment of otorrhea.[26] The study included 139 affected ears of which 102 (74 percent) completed the trial. There was no significant difference between the two treatment groups in improvement in otorrhea (67 percent for aluminum acetate versus 68 percent for gentamicin). No resistant organisms to aluminum acetate were reported; however, 12 gentamicin-treated ears had gentamicin resistant organisms and one patient developed a gentamicin-resistant *Pseudomonas*.

SUMMARY

The products in this review contain various combinations of antiseptic, anesthetic, astringent, anti-inflammatory, and analgesic compounds and are used topically for the treatment of otitis externa, as adjunct therapy in the treatment of acute otitis media, and to facilitate cerumen removal from the ear canal.

The American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) recommends topical preparations for initial therapy of uncomplicated acute otitis externa, while systemic antimicrobial therapy should be used if there is extension outside the ear canal, or if specific host factors are present.

Similar results have been reported with any of the choices of topical agents including acidifying agents, antibiotics, antibiotic and steroid combinations, or antifungal agents in the treatment of otitis externa. In addition, for cerumen removal, no specific agent was found to be superior to another and none were superior to either saline or water.

All products in this review are contraindicated in persons with perforated tympanic membranes or unexplained discharge from the ear.

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